

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/GB05/001079

International filing date: 22 March 2005 (22.03.2005)

Document type: Certified copy of priority document

Document details: Country/Office: GB
Number: 0406450.7
Filing date: 23 March 2004 (23.03.2004)

Date of receipt at the International Bureau: 22 April 2005 (22.04.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse



PCT/GB 2005 / 0 0 1 0 7 9



INVESTOR IN PEOPLE

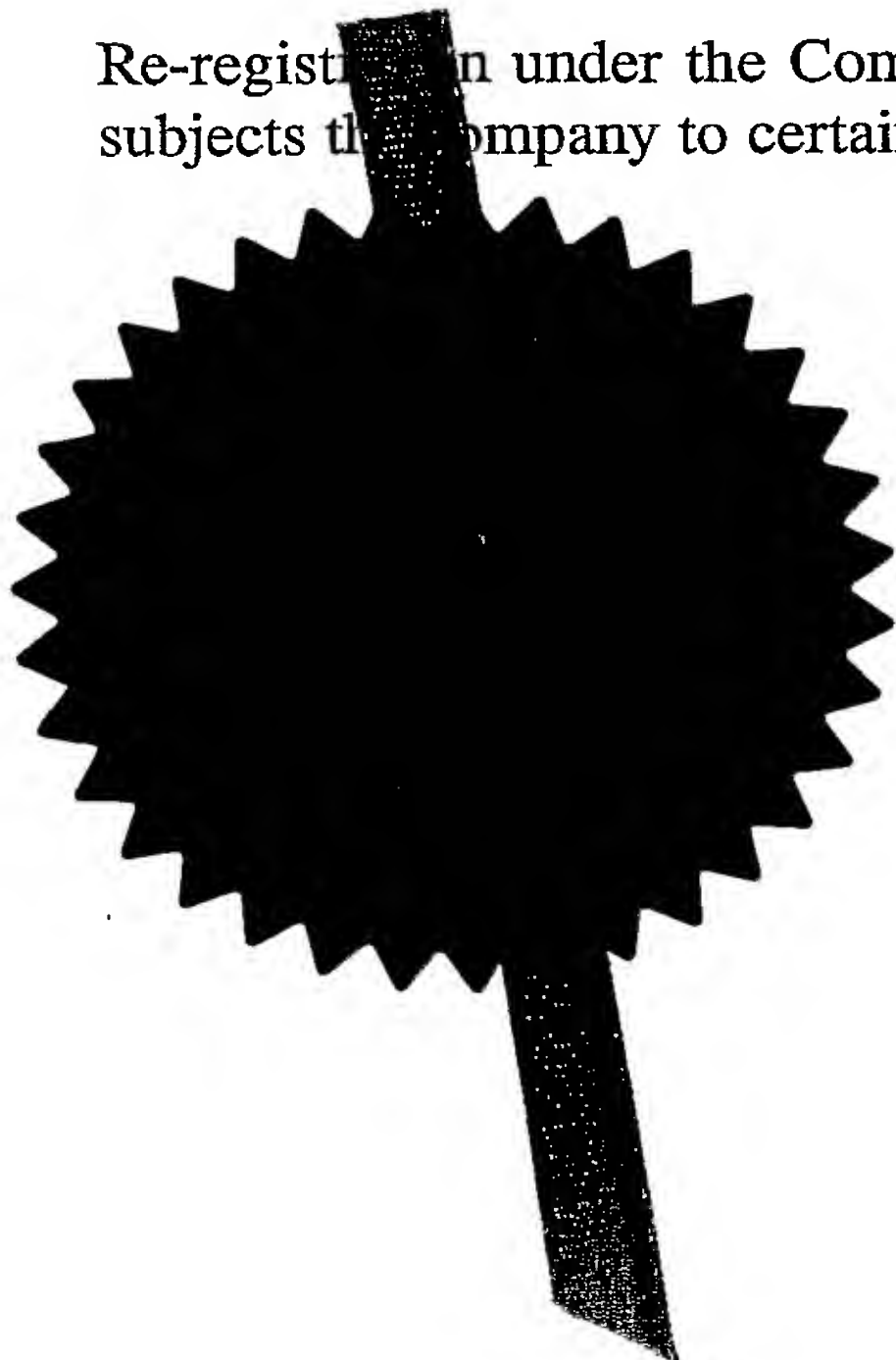
The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

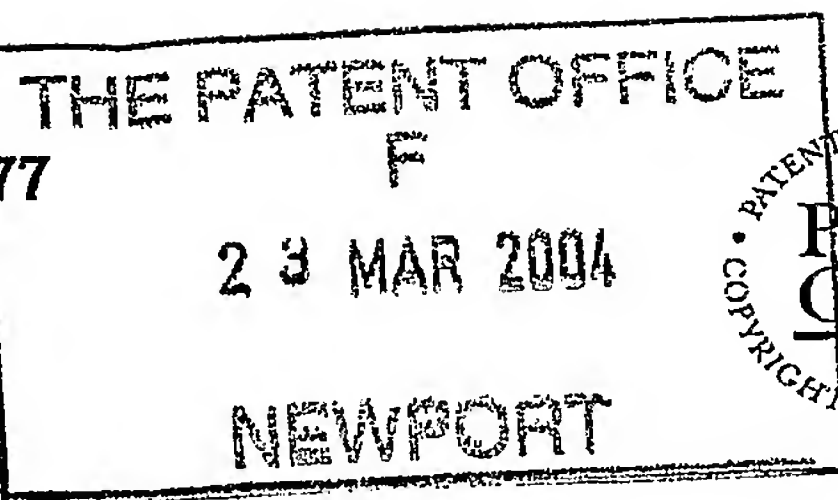
Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.



Signed

Stephen Hordley

Dated 12 April 2005



23MAR04 E883059-1 002934
P01/7700 0.00-0406450.7 NONE

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference 101406-1

2. Patent application number
(The Patent Office will fill in this part)

0406450.7

23 MAR 2004

3. Full name, address and postcode of the or of each applicant (underline all surnames)

AstraZeneca AB
SE-151 85 Sodertalje
Sweden

7822448003

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

Sweden

4. Title of the invention

COMBINATION THERAPY

5. Name of your agent (if you have one)

Tracy Anne BURNS

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

AstraZeneca
Global Intellectual Property
P O Box 272
Mereside, Alderley Park
Macclesfield,
Cheshire SK10 4GR

Patents ADP number (if you know it)

8179707001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country

Priority application number
(if you know it)

Date of filing
(day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing
(day / month / year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

- a) any applicant named in part 3 is not an inventor, or
 - b) there is an inventor who is not named as an applicant, or
 - c) any named applicant is a corporate body.
- See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form

Description 15 —

Claim(s) 2 —

Abstract

Drawing(s) 2 + 2 *2*

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

Request for preliminary examination and search (*Patents Form 9/77*)

Request for substantive examination (*Patents Form 10/77*)

Any other documents
(please specify)

11. I/We request the grant of a patent on the basis of this application.

Signature

S. A. Douglas

Date

22/03/2004

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs Shirley A Douglas - 01625 510057

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

- a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.*
- b) Write your answers in capital letters using black ink or you may type them.*
- c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.*
- d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.*
- e) Once you have filled in the form you must remember to sign and date it.*
- f) For details of the fee and ways to pay please contact the Patent Office.*

COMBINATION THERAPY

The present invention relates to a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is optionally being treated with ionising radiation, particularly a method for the treatment of a cancer, particularly a cancer involving a solid tumour, which comprises the administration of AZD2171 in combination with a platinum anti-tumour agent; to a pharmaceutical composition comprising AZD2171 and a platinum anti-tumour agent; to a combination product comprising AZD2171 and a platinum anti-tumour agent for use in a method of treatment of a human or animal body by therapy; to a kit comprising AZD2171 and a platinum anti-tumour agent; to the use of AZD2171 and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is optionally being treated with ionising radiation.

Normal angiogenesis plays an important role in a variety of processes including embryonic development, wound healing and several components of female reproductive function. Undesirable or pathological angiogenesis has been associated with disease states including diabetic retinopathy, psoriasis, cancer, rheumatoid arthritis, atheroma, Kaposi's sarcoma and haemangioma (Fan et al, 1995, Trends Pharmacol. Sci. 16: 57-66; Folkman, 1995, Nature Medicine 1: 27-31). Alteration of vascular permeability is thought to play a role in both normal and pathological physiological processes (Cullinan-Bove et al, 1993, Endocrinology 133: 829-837; Senger et al, 1993, Cancer and Metastasis Reviews, 12: 303-324). Several polypeptides with *in vitro* endothelial cell growth promoting activity have been identified including, acidic and basic fibroblast growth factors (aFGF & bFGF) and vascular endothelial growth factor (VEGF). By virtue of the restricted expression of its receptors, the growth factor activity of VEGF, in contrast to that of the FGFs, is relatively specific towards endothelial cells. Recent evidence indicates that VEGF is an important stimulator of both normal and pathological angiogenesis (Jakeman et al, 1993, Endocrinology, 133: 848-859; Kolch et al, 1995, Breast Cancer Research and Treatment, 36:139-155) and vascular permeability (Connolly et al, 1989, J. Biol. Chem. 264: 20017-20024). Antagonism of VEGF action by sequestration of VEGF with antibody can result in inhibition of tumour growth (Kim et al, 1993, Nature 362: 841-844).

Receptor tyrosine kinases (RTKs) are important in the transmission of biochemical signals across the plasma membrane of cells. These transmembrane molecules characteristically consist of an extracellular ligand-binding domain connected through a segment in the plasma

membrane to an intracellular tyrosine kinase domain. Binding of ligand to the receptor results in stimulation of the receptor-associated tyrosine kinase activity which leads to phosphorylation of tyrosine residues on both the receptor and other intracellular molecules. These changes in tyrosine phosphorylation initiate a signalling cascade leading to a variety of cellular responses.

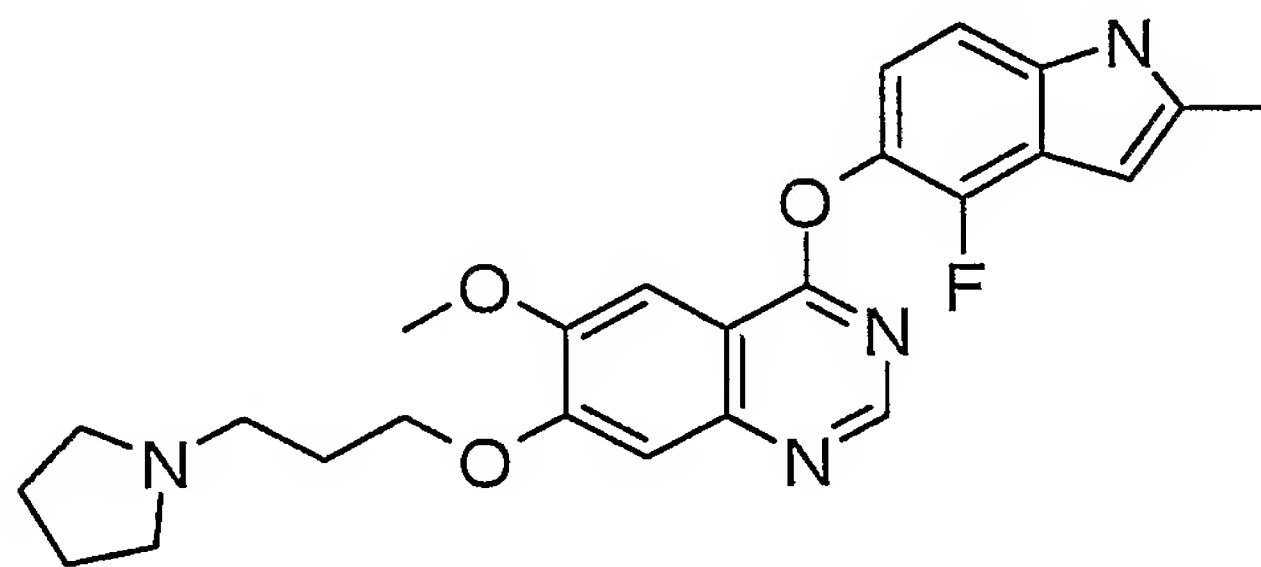
5 To date, at least nineteen distinct RTK subfamilies, defined by amino acid sequence homology, have been identified. One of these subfamilies is presently comprised by the *fms*-like tyrosine kinase receptor, Flt-1 (also referred to as VEGFR-1), the kinase insert domain-containing receptor, KDR (also referred to as VEGFR-2 or Flk-1), and another *fms*-like tyrosine kinase receptor, Flt-4. Two of these related RTKs, Flt-1 and KDR, have been shown to bind VEGF
10 with high affinity (De Vries et al, 1992, *Science* 255: 989-991; Terman et al, 1992, *Biochem Biophys. Res. Comm.* 1992, 187: 1579-1586). Binding of VEGF to these receptors expressed in heterologous cells has been associated with changes in the tyrosine phosphorylation status of cellular proteins and calcium fluxes.

VEGF is a key stimulus for vasculogenesis and angiogenesis. This cytokine induces a
15 vascular sprouting phenotype by inducing endothelial cell proliferation, protease expression and migration, and subsequent organisation of cells to form a capillary tube (Keck, P.J., Hauser, S.D., Krivi, G., Sanzo, K., Warren, T., Feder, J., and Connolly, D.T., *Science* (Washington DC), 246: 1309-1312, 1989; Lamoreaux, W.J., Fitzgerald, M.E., Reiner, A., Hasty, K.A., and Charles, S.T., *Microvasc. Res.*, 55: 29-42, 1998; Pepper, M.S., Montesano,
20 R., Mandroita, S.J., Orci, L. and Vassalli, J.D., *Enzyme Protein*, 49: 138-162, 1996.). In addition, VEGF induces significant vascular permeability (Dvorak, H.F., Detmar, M., Claffey, K.P., Nagy, J.A., van de Water, L., and Senger, D.R., (*Int. Arch. Allergy Immunol.*, 107: 233-235, 1995; Bates, D.O., Heald, R.I., Curry, F.E. and Williams, B. *J. Physiol. (Lond.)*, 533: 263-272, 2001), promoting formation of a hyper-permeable, immature vascular network which
25 is characteristic of pathological angiogenesis.

It has been shown that activation of KDR alone is sufficient to promote all of the major phenotypic responses to VEGF, including endothelial cell proliferation, migration, and survival, and the induction of vascular permeability (Meyer, M., Clauss, M., Lepple-Wienhues, A., Waltenberger, J., Augustin, H.G., Ziche, M., Lanz, C., Büttner, M., Rziha, H-J., and Dehio, C.,
30 *EMBO J.*, 18: 363-374, 1999; Zeng, H., Sanyal, S. and Mukhopadhyay, D., *J. Biol. Chem.*, 276: 32714-32719, 2001; Gille, H., Kowalski, J., Li, B., LeCouter, J., Moffat, B, Zioncheck, T.F., Pelletier, N. and Ferrara, N., *J. Biol. Chem.*, 276: 3222-3230, 2001).

Quinazoline derivatives which are inhibitors of VEGF receptor tyrosine kinase are described in International Patent Application Publication No. WO 00/47212. AZD2171 is described in WO 00/47212 and is Example 240 therein. AZD2171 is 4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline:

5,



AZD2171

AZD2171 shows excellent activity in the *in vitro* (a) enzyme and (b) HUVEC assays that are described in WO 00/47212 (pages 80-83). The AZD2171 IC₅₀ values for inhibition of isolated KDR (VEGFR-2) and Flt-1 (VEGFR-1) tyrosine kinase activities in the enzyme assay were <2 nM and 5 ± 2 nM respectively. AZD2171 inhibits VEGF-stimulated endothelial cell proliferation potently (IC₅₀ value of 0.4 ± 0.2 nM in the HUVEC assay), but does not inhibit basal endothelial cell proliferation appreciably at a > 1250 fold greater concentration (IC₅₀ value is > 500 nM). The growth of a Calu-6 tumour xenograft in the *in vivo* solid tumour model described in WO 00/47212 (page 83) was inhibited by 49%^{**}, 69%^{***} and 91%^{***} following 28 days of once-daily oral treatment with 1.5, 3 and 6 mg/kg/day AZD2171 respectively (P^{**} < 0.01, P^{***} < 0.0001; one-tailed t test). AZD2171 has been shown to elicit broad-spectrum anti-tumour activity in a range of models following once-daily oral administration.

In WO 00/47212 it is stated that compounds of the invention:

“may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment.”

WO 00/47212 then goes on to describe examples of such conjoint treatment including surgery, radiotherapy and various types of chemotherapeutic agent.

Nowhere in WO 00/47212 is the specific combination of AZD2171 and a platinum anti-tumour agent suggested.

Nowhere in WO 00/47212 does it state that use of any compound of the invention therein with other treatments will produce surprisingly beneficial effects.

5 Unexpectedly and surprisingly we have now found that the particular compound AZD2171 used in combination with a particular selection from the broad description of combination therapies listed in WO 00/47212, namely with a platinum anti-tumour agent, produces significantly better effects than any one of AZD2171 and a platinum anti-tumour agent used alone. In particular, AZD2171 used in combination with a platinum anti-tumour
10 agent produces significantly better effects on solid tumours than any one of AZD2171 and a platinum anti-tumour agent used alone.

A platinum anti-tumour agent is any anti-tumour agent containing platinum. Platinum anti-tumour agents include cisplatin, carboplatin, oxaliplatin, nedaplatin, lobaplatin, satraplatin and AMD473.

15 Anti-cancer effects of a method of treatment of the present invention include, but are not limited to, anti-tumour effects, the response rate, the time to disease progression and the survival rate. Anti-tumour effects of a method of treatment of the present invention include but are not limited to, inhibition of tumour growth, tumour growth delay, regression of tumour, shrinkage of tumour, increased time to regrowth of tumour on cessation of treatment,
20 slowing of disease progression. It is expected that when a method of treatment of the present invention is administered to a warm-blooded animal such as a human, in need of treatment for cancer, with or without a solid tumour, said method of treatment will produce an effect, as measured by, for example, one or more of: the extent of the anti-tumour effect, the response rate, the time to disease progression and the survival rate. Anti-cancer effects include
25 prophylactic treatment as well as treatment of existing disease.

According to the present invention there is provided a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective
30 amount of a platinum anti-tumour agent.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises

administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a platinum anti-tumour agent.

According to a further aspect of the present invention there is provided a method for
5 the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a platinum anti-tumour agent.

According to a further aspect of the present invention there is provided a method for
10 the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a platinum anti-tumour agent; wherein AZD2171 and a platinum anti-tumour agent may each optionally be administered together with a
15 pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a platinum anti-tumour
20 agent; wherein AZD2171 and a platinum anti-tumour agent may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a
25 pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a platinum anti-tumour agent; wherein AZD2171 and a platinum anti-tumour agent may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the invention there is provided a pharmaceutical
30 composition which comprises AZD2171 or a pharmaceutically acceptable salt thereof, and a platinum anti-tumour agent, in association with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a combination product comprising AZD2171 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent, for use in a method of treatment of a human or animal body by therapy.

According to a further aspect of the present invention there is provided a kit
5 comprising AZD2171 or a pharmaceutically acceptable salt thereof, and a platinum anti-tumour agent.

According to a further aspect of the present invention there is provided a kit comprising:

- a) AZD2171 or a pharmaceutically acceptable salt thereof in a first unit dosage form;
- 10 b) a platinum anti-tumour agent in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

- a) AZD2171 or a pharmaceutically acceptable salt thereof, together with a pharmaceutically
15 acceptable excipient or carrier, in a first unit dosage form;
- b) a platinum anti-tumour agent together with a pharmaceutically acceptable excipient or carrier, in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided the use of
20 AZD2171 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human.

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent in
25 the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human.

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an anti-tumour effect in a
30 warm-blooded animal such as a human.

According to a further aspect of the present invention there is provided a therapeutic combination treatment comprising the administration of an effective amount of AZD2171 or a

pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable excipient or carrier, and the simultaneous, sequential or separate administration of an effective amount of a platinum anti-tumour agent, wherein a platinum anti-tumour agent may optionally be administered together with a pharmaceutically acceptable excipient or carrier, to a warm-blooded animal such as a human in need of such therapeutic treatment. Such therapeutic treatment includes an antiangiogenic and/or vascular permeability effect, an anti-cancer effect and an anti-tumour effect.

A combination treatment of the present invention as defined herein may be achieved by way of the simultaneous, sequential or separate administration of the individual components of said treatment. A combination treatment as defined herein may be applied as a sole therapy or may involve surgery or radiotherapy or an additional chemotherapeutic agent in addition to a combination treatment of the invention.

Surgery may comprise the step of partial or complete tumour resection, prior to, during or after the administration of the combination treatment with AZD2171 described herein.

Other chemotherapeutic agents for optional use with a combination treatment of the present invention include those described in WO 00/47212 which is incorporated herein by reference. Such chemotherapy may cover five main categories of therapeutic agent:

(i) other antiangiogenic agents including vascular targeting agents;

(ii) cytostatic agents;

(iii) biological response modifiers (for example interferon);

(iv) antibodies (for example edrecolomab); and

(v) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology; and other categories of agent are:

(vi) antisense therapies;

(vii) gene therapy approaches; and

(ix) immunotherapy approaches.

Particular examples of chemotherapeutic agents for use with a combination treatment of the present invention are raltitrexed, etoposide, vinorelbine, paclitaxel, docetaxel, gemcitabine, irinotecan (CPT-11) and 5-fluorouracil (5-FU, (including capecitabine)) ; such combinations are expected to be particularly useful for the treatment of cancer of the lung, head and neck, colon, rectum, oesophagus, stomach, cervix, ovary, skin, breast, bladder and pancreas.

The administration of a triple combination of AZD2171, a platinum anti-tumour agent and ionising radiation may produce effects, such as anti-tumour effects, greater than those achieved with any of AZD2171, a platinum anti-tumour agent and ionising radiation used alone, greater than those achieved with the combination of AZD2171 and a platinum anti-tumour agent, greater than those achieved with the combination of AZD2171 and ionising radiation, greater than those achieved with the combination of a platinum anti-tumour agent and ionising radiation.

According to the present invention there is provided a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a platinum anti-tumour agent and before, after or simultaneously with an effective amount of ionising radiation.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a platinum anti-tumour agent and before, after or simultaneously with an effective amount of ionising radiation.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a platinum anti-tumour agent and before, after or simultaneously with an effective amount of ionising radiation.

According to a further aspect of the present invention there is provided a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a platinum anti-tumour agent and before, after or simultaneously with an effective amount of ionising radiation, wherein AZD2171 and a platinum anti-tumour agent may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a platinum anti-tumour agent and before, after or simultaneously with an effective amount of ionising radiation, wherein AZD2171 and a platinum anti-tumour agent may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a platinum anti-tumour agent and before, after or simultaneously with an effective amount of ionising radiation, wherein AZD2171 and a platinum anti-tumour agent may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

According to a further aspect of the present invention there is provided a therapeutic combination treatment comprising the administration of an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable excipient or carrier, and the administration of an effective amount of a platinum anti-tumour agent, optionally together with a pharmaceutically acceptable excipient or carrier

and the administration of an effective amount of ionising radiation, to a warm-blooded animal such as a human in need of such therapeutic treatment wherein the AZD2171, a platinum anti-tumour agent and ionising radiation may be administered simultaneously, sequentially or separately and in any order.

5 A warm-blooded animal such as a human which is being treated with ionising radiation means a warm-blooded animal such as a human which is treated with ionising radiation before, after or at the same time as the administration of a medicament or combination treatment comprising AZD2171 and a platinum anti-tumour agent. For example said ionising radiation may be given to said warm-blooded animal such as a human within the period of a week before
10 to a week after the administration of a medicament or combination treatment comprising AZD2171 and a platinum anti-tumour agent. This means that AZD2171, a platinum anti-tumour agent and ionising radiation may be administered separately or sequentially in any order, or may be administered simultaneously. The warm-blooded animal may experience the effect of each of AZD2171, a platinum anti-tumour agent and radiation simultaneously.

15 According to one aspect of the present invention the ionising radiation is administered before one of AZD2171 and a platinum anti-tumour agent or after one of AZD2171 and a platinum anti-tumour agent.

 According to one aspect of the present invention the ionising radiation is administered before both AZD2171 and a platinum anti-tumour agent or after both AZD2171 and a
20 platinum anti-tumour agent.

 According to one aspect of the present invention AZD2171 is administered to a warm-blooded animal after the animal has been treated with ionising radiation.

 According to another aspect of the present invention the effect of a method of treatment of the present invention is expected to be at least equivalent to the addition of the
25 effects of each of the components of said treatment used alone, that is, of each of AZD2171 and a platinum anti-tumour agent used alone or of each of AZD2171, a platinum anti-tumour agent and ionising radiation used alone.

 According to another aspect of the present invention the effect of a method of treatment of the present invention is expected to be greater than the addition of the effects of
30 each of the components of said treatment used alone, that is, of each of AZD2171 and a platinum anti-tumour agent used alone or of each of AZD2171, a platinum anti-tumour agent and ionising radiation used alone.

According to another aspect of the present invention the effect of a method of treatment of the present invention is expected to be a synergistic effect.

According to the present invention a combination treatment is defined as affording a synergistic effect if the effect is therapeutically superior, as measured by, for example, the extent of the response, the response rate, the time to disease progression or the survival period, to that achievable on dosing one or other of the components of the combination treatment at its conventional dose. For example, the effect of the combination treatment is synergistic if the effect is therapeutically superior to the effect achievable with AZD2171 or a platinum anti-tumour agent or ionising radiation alone. Further, the effect of the combination treatment is synergistic if a beneficial effect is obtained in a group of patients that does not respond (or responds poorly) to AZD2171 or a platinum anti-tumour agent or ionising radiation alone. In addition, the effect of the combination treatment is defined as affording a synergistic effect if one of the components is dosed at its conventional dose and the other component(s) is/are dosed at a reduced dose and the therapeutic effect, as measured by, for example, the extent of the response, the response rate, the time to disease progression or the survival period, is equivalent to that achievable on dosing conventional amounts of the components of the combination treatment. In particular, synergy is deemed to be present if the conventional dose of AZD2171 or a platinum anti-tumour agent or ionising radiation may be reduced without detriment to one or more of the extent of the response, the response rate, the time to disease progression and survival data, in particular without detriment to the duration of the response, but with fewer and/or less troublesome side-effects than those that occur when conventional doses of each component are used.

As stated above the combination treatments of the present invention as defined herein are of interest for their antiangiogenic and/or vascular permeability effects. Angiogenesis and/or an increase in vascular permeability is present in a wide range of disease states including cancer (including leukaemia, multiple myeloma and lymphoma), diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, lymphoedema, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation including age-related macular degeneration. Combination treatments of the present invention are expected to be particularly useful in the prophylaxis and treatment of diseases such as cancer and Kaposi's sarcoma.

In particular such combination treatments of the invention are expected to slow advantageously the growth of primary and recurrent solid tumours of, for example, the colon, pancreas, bladder, breast, prostate, lungs and skin. More especially combination treatments of the present invention are expected to slow advantageously the growth of tumours in colorectal cancer and in
5 lung cancer, for example mesothelioma and non-small cell lung cancer (NSCLC). More particularly such combination treatments of the invention are expected to inhibit any form of cancer associated with VEGF including leukaemia, multiple myeloma and lymphoma and also, for example, to inhibit the growth of those primary and recurrent solid tumours which are associated with VEGF, especially those tumours which are significantly dependent on VEGF for
10 their growth and spread, including for example, certain tumours of the colon (including rectum), pancreas, bladder, breast, prostate, lung, vulva, skin and particularly NSCLC.

In another aspect of the present invention AZD2171 and a platinum anti-tumour agent, optionally with ionising radiation, are expected to inhibit the growth of those primary and recurrent solid tumours which are associated with VEGF especially those tumours which are
15 significantly dependent on VEGF for their growth and spread.

The compositions described herein may be in a form suitable for oral administration, for example as a tablet or capsule, for nasal administration or administration by inhalation, for example as a powder or solution, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) for example as a sterile solution, suspension or
20 emulsion, for topical administration for example as an ointment or cream, for rectal administration for example as a suppository or the route of administration may be by direct injection into the tumour or by regional delivery or by local delivery. In other embodiments of the present invention the AZD2171 of the combination treatment may be delivered endoscopically, intratracheally, intralesionally, percutaneously, intravenously, subcutaneously,
25 intraperitoneally or intratumourally. Preferably AZD2171 is administered orally. In general the compositions described herein may be prepared in a conventional manner using conventional excipients. The compositions of the present invention are advantageously presented in unit dosage form.

AZD2171 will normally be administered to a warm-blooded animal at a unit dose
30 within the range 1-50mg per square metre body area of the animal, for example approximately 0.03-1.5 mg/kg in a human. A unit dose in the range, for example, 0.01-1.5mg/kg, preferably 0.03-0.5mg/kg is envisaged and this is normally a therapeutically-effective dose. A unit dosage

form such as a tablet or capsule will usually contain, for example 1-50mg of active ingredient. Preferably a daily dose in the range of 0.03-0.5mg/kg is employed.

Platinum anti-tumour agents may be dosed according to known routes of administration and dosages.

- 5 For example cisplatin may be administered as a single intravenous infusion over a period of 6-8 hours at a dose of 40-120mg/m² every 3-4 weeks. Alternatively for example cisplatin may be administered as a single intravenous infusion over a period of 6-8 hours at a dose of 15-20mg/m² daily for up to 5 days every 3-4 weeks.

- For example carboplatin may be administered as a single short-term intravenous
10 infusion over a period of 15-60 minutes at a dose of 250-400mg/m² every 4 weeks.

For example oxaliplatin may be administered by intravenous infusion over a period of 2-6 hours at a dose of about 85mg/m² every 2 weeks.

- The size of the dose of each therapy which is required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied depending on the
15 host treated, the route of administration and the severity of the illness being treated.

Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient. For example, it may be necessary or desirable to reduce the above-mentioned doses of the components of the combination treatments in order to reduce toxicity.

- Radiotherapy may be administered according to the known practices in clinical
20 radiotherapy. The dosages of ionising radiation will be those known for use in clinical radiotherapy. The radiation therapy used will include for example the use of γ -rays, X-rays, and/or the directed delivery of radiation from radioisotopes. Other forms of DNA damaging factors are also included in the present invention such as microwaves and UV-irradiation. For example X-rays may be dosed in daily doses of 1.8-2.0Gy, 5 days a week for 5-6 weeks.
- 25 Normally a total fractionated dose will lie in the range 45-60Gy. Single larger doses, for example 5-10Gy may be administered as part of a course of radiotherapy. Single doses may be administered intraoperatively. Hyperfractionated radiotherapy may be used whereby small doses of X-rays are administered regularly over a period of time, for example 0.1Gy per hour over a number of days. Dosage ranges for radioisotopes vary widely, and depend on the half-
30 life of the isotope, the strength and type of radiation emitted, and on the uptake by cells.

As stated above the size of the dose of each therapy which is required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied

depending on the host treated, the route of administration and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient. For example, it may be necessary or desirable to reduce the above-mentioned doses of the components of the combination treatments in order to reduce toxicity.

The present invention relates to combinations of a platinum anti-tumour agent with AZD2171 or with a salt of AZD2171.

Salts of AZD2171 for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of AZD2171 and its pharmaceutically acceptable salts. Pharmaceutically acceptable salts may, for example, include acid addition salts. Such acid addition salts include for example salts with inorganic or organic acids affording pharmaceutically acceptable anions such as with hydrogen halides or with sulphuric or phosphoric acid, or with trifluoroacetic, citric or maleic acid. In addition pharmaceutically acceptable salts may be formed with an inorganic or organic base which affords a pharmaceutically acceptable cation. Such salts with inorganic or organic bases include for example an alkali metal salt, such as a sodium or potassium salt and an alkaline earth metal salt such as a calcium or magnesium salt.

AZD2171 may be synthesised according to the processes described in WO 00/47212, in particular those described in Example 240 of WO 00/47212.

Platinum anti-tumour agents are commercially available.

The following tests may be used to demonstrate the activity of AZD2171 in combination with a platinum anti-tumour agent.

Human lung cancer (NSCLC) xenograft model (Calu-6)

Athymic nude mice are injected subcutaneously (s.c.) with Calu 6 human tumour cells. Treatment begins after 10 days when tumours are established (tumour volume = 350-400 mm³). Groups of animals (n = 9-10 per group) are randomized to receive a single treatment with cisplatin (4 mg/kg i.p.) on day of randomisation, or treatment with AZD2171 (0.5mg/kg or 1.5mg/kg, p.o. daily) for the duration of the experiment, or drug vehicles only. An additional group of animals (n = 9-10) receives a combination of cisplatin and AZD2171, using the same doses and schedules as used for single agent treatment. On days where animals

received both AZD2171 and cisplatin the cisplatin was administered 2 hours after oral dosing with AZD2171.

Animals in all groups are sacrificed when the control tumours reach approximately 2.0 cm³. Tumour size is assessed throughout the experiment by using caliper measurements.

5 Antitumour effects are determined by comparing tumour growth in the drug-treated groups with tumour growth in the vehicle treated groups. Additionally, the effects of combination treatment are assessed by comparing tumour growth in the group of animals receiving cisplatin plus AZD2171 with the tumour growth in the groups where animals received single agent therapy alone.

10 Statistical significance was evaluated using a one-tailed two-sample t-test.

The results are shown in Figures 1 and 2.

The growth of the tumours was inhibited significantly more by the combination of the two agents AZD2171 (1.5 or 0.5mg/kg) and cisplatin (4mg/kg on day of randomisation) than by either agent alone at the same doses.

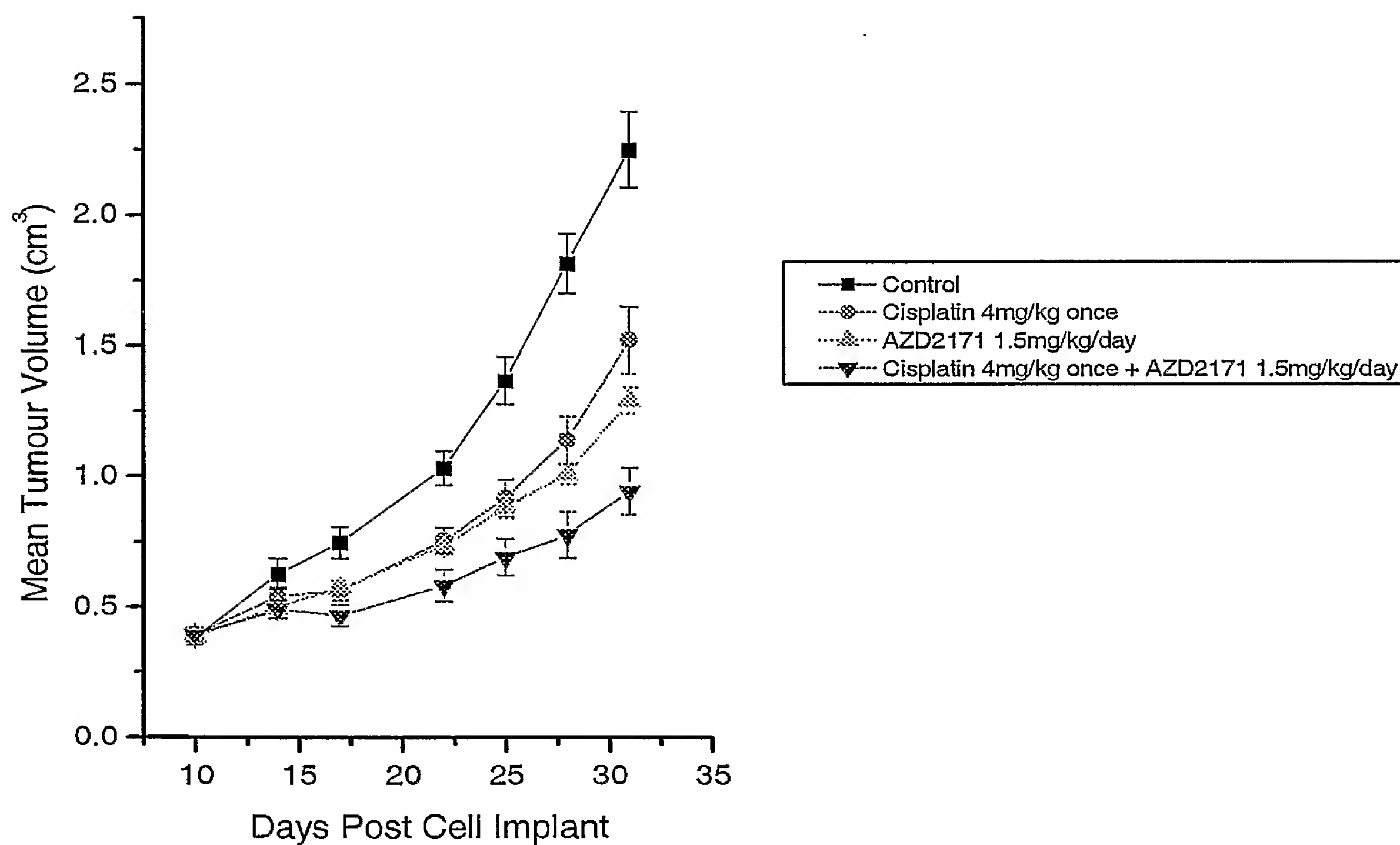
15 An analogous experiment may be used to look at the combination of AZD2171, a platinum anti-tumour agent and ionising radiation.

CLAIMS

1. Use of AZD2171 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an
5 antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human.
2. Use of AZD2171 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an anti-cancer
10 effect in a warm-blooded animal such as a human.
3. Use of AZD2171 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human.
15
4. Use of AZD2171 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is being treated with ionising radiation.
20
5. Use of AZD2171 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human which is being treated with ionising radiation.
- 25 6. Use of AZD2171 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human which is being treated with ionising radiation.
7. Use according to any one of claims 1-6 wherein the platinum anti-tumour agent is
30 cisplatin.
8. Use according to any one of claims 1-6 wherein the platinum anti-tumour agent is carboplatin.

9. Use according to any one of claims 1-6 wherein the platinum anti-tumour agent is oxaliplatin.
- 5 10. A pharmaceutical composition which comprises AZD2171 or a pharmaceutically acceptable salt thereof, and a platinum anti-tumour agent, in association with a pharmaceutically acceptable excipient or carrier.
11. A kit comprising AZD2171 or a pharmaceutically acceptable salt thereof, and a
10 platinum anti-tumour agent.
12. A method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof,
15 before, after or simultaneously with an effective amount of a platinum anti-tumour agent.
13. A method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof,
20 before, after or simultaneously with an effective amount of a platinum anti-tumour agent and before, after or simultaneously with an effective amount of ionising radiation.

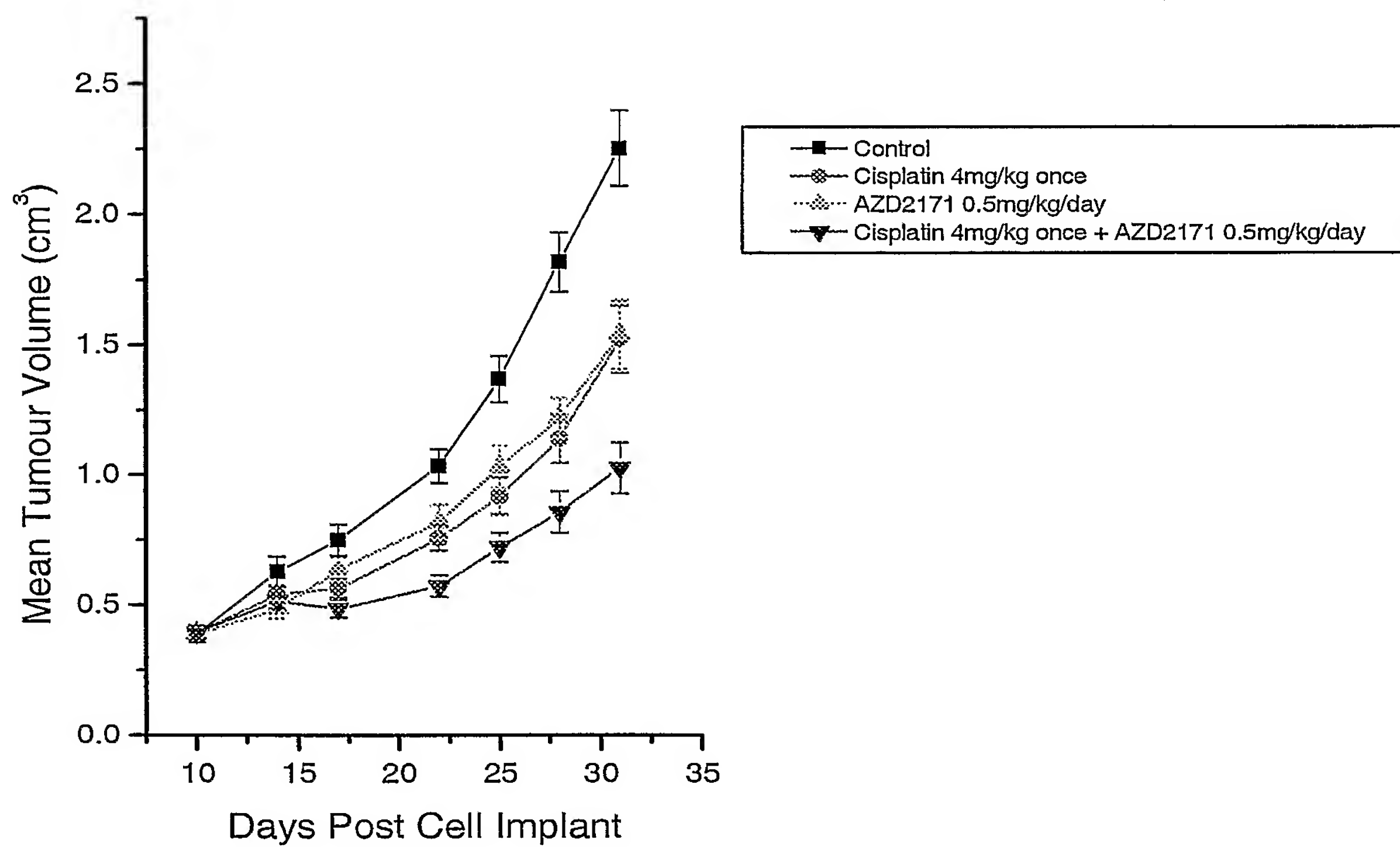


**Figure 1**

Cisplatin 4mg/kg vs Cisplatin 4mg/kg + AZD2171 1.5mg/kg $p=0.0003$

AZD2171 1.5mg/kg vs Cisplatin 4mg/kg + AZD2171 1.5mg/kg $p=0.0014$



**Figure 2**

Cisplatin 4mg/kg vs Cisplatin 4mg/kg + AZD2171 0.5mg/kg $p=0.0087$

AZD2171 0.5mg/kg vs Cisplatin 4mg/kg + AZD2171 0.5mg/kg $p=0.0029$

THE PATENT OFFICE

13 APR 2005

Received in Patents
International Unit

